stored and not infrequently satisfactory results were obtained.

The study of alkalosis, its production and treatment, is most interesting, and is unquestionably one of the major contributions of modern times to gastro-intestinal surgery.

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DOCTOR PULFORD (closing).—Alkalosis now, like acidosis in the past, should bring to mind a definite clinical and laboratory picture. The purely medical aspects of this problem demand our attention, and this, as with almost all modern medical procedure, requires teamwork in its proper handling.

Clinically the two best aids to recognizing alkalosis early are the finding of a very low blood pressure and extreme prostration. In the medical treatment of alkalosis a prompt administration of water, salt and glucose may either tide over and make operation unnecessary, or change a poor surgical risk to a safe one, if secondary operation is necessary.

The chief mistakes in the medical management of these cases are: too frequent lavage and the administration of alkalis.

Advanced grades of alkalosis are seldom permitted at present, as a low plasma sodium chlorid is found early in any upper intestinal obstruction case and a 3 per cent sodium chlorid solution given intravenously long before the plasma $CO_2$ rises to any extent.

Our cases, therefore, emphasize the fact that there is a clinical syndrome and accurate laboratory diagnostic method and a specifically indicated and efficacious medical treatment for a frequently overlooked toxemia called "alkalosis."

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# TOXIC GOITER *

## THE IMPORTANCE OF A DIFFERENTIAL DIAGNOSIS

*By* A. B. COOKE, M. D.
*Los Angeles*

DISCUSSION *by Philip K. Gilman, M. D., San Francisco; Carl L. Hoag, M. D., San Francisco; A. S. Lobingier, M. D., Los Angeles.*

PRIMARILY goiter is a clinical problem. Many fascinating questions of scientific and controversial interest are also involved, to be sure; but these are of secondary importance. What we seek first to know about the individual case is what form of the disease it represents and what method of treatment promises the surest and safest relief. Simplicity of classification undoubtedly promotes clear thinking and correct conclusions on these fundamental points.

From the clinical standpoint a goiter is either toxic or nontoxic. In the former, active treatment is always required; in the latter, the matter of treatment is often decided by the patient.

### FAMILIAR TYPES OF TOXIC GOITER

The purpose of this paper is to limit itself to a consideration of the first-named class, *i. e.*, toxic goiter, and is further limited to its two most familiar types, hyperplastic or exophthalmic goiter, and toxic adenoma.

Are these two types of thyroid disease in reality clinical entities? Is the output of the hyperplastic thyroid identical in kind with that of the overactive adenomatous gland? Or does the hyperthyroidism of the one differ in essence from that of the other so that the matter of their clinical differentiation may properly concern us?

In the present state of our knowledge we cannot turn to chemistry for the answers to these questions, though, as Plummer suggests, when methods of investigation have been sufficiently perfected it may well prove that the several differences observed in the phenomena of the two forms are due to some structural variation in the composition or arrangement of the thyroxin molecule.

We must needs, therefore, have recourse to the phenomena themselves for the answers. If these are critically examined and fairly adjudged, separately and as a whole, the conclusion is inevitable, I think, that the difference between the hyperplastic goiter and the toxic adenoma is more than a difference of degree. It is scarcely conceivable that the same cause could give rise to disease syndromes so markedly and invariably different both in developmental sequence and in actual manifestations. This view, it must be admitted, is not universally accepted. But the question, if raised at all in current literature, is usually disposed of with simply a passing statement of the writer's opinion. Nowhere do we find it discussed with the fullness and seriousness its importance would seem to merit.

### TABLE OF DIFFERENTIAL POINTS

The foregoing is a table listing the salient differential points in parallel columns:

Any one or all of the foregoing differential points may be modified and the clinical picture confused when, as is not infrequently true, both types of pathology are present in the same case. The diagnosis of hyperthyroidism may, of course, be made readily in such a case; but a clear-cut differentiation may be very difficult or quite impossible. This fact should be kept constantly in mind when the individual patient is being studied.

Let us consider now a little more fully the two last points of the differential scheme, namely, lymphocytosis, and iodin therapy.

### LYMPHOCYTOSIS AND LEUKOPENIA

*Lymphocytosis.*—More than a generation ago the great pioneer student of the goiter problem, Kocher, stated that the blood in true Graves' disease was characterized by both lymphocytosis and leukopenia. A few years later Halsted announced that he had verified Kocher's observation. Slight impression seems to have been made, however, for, in spite of the prestige of these two illustrious names, the literature of the past twenty-five years contains nothing notable on the subject.

Several years ago my attention was caught by a passing allusion of de Quervain to the original observation of Kocher, and I determined to investigate it for myself. Fortunately routine blood examinations are required for all patients by modern hospitals; these histories and those of private patients made available a considerable amount of data.

Without introducing dry statistics let me say briefly that I am convinced that Kocher's finding was and is correct, *i. e.*, that in true, uncomplicated Graves' disease the blood picture shows both a lymphocytosis and a leukopenia. The white cell

* Read before the General Surgery Section of the California Medical Association at its Fifty-Seventh Annual Session April 30 to May 3, 1928.

*Differential Diagnosis of Exophthalmic Goiter and Toxic Adenoma*

| Exophthalmic (Hyperplastic) Goiter | Toxic Adenoma |
|---|---|
| 1. Exophthalmos (60 to 80 per cent). | 1. No exophthalmos. |
| 2. Goiter of soft, uniform consistence, usually symmetrical. | 2. Firm, nodular, seldom symmetrical. |
| 3. Etiology—Uncertain; probably psychic trauma. | 3. Etiology—Endemic; probably iodin deficiency. |
| 4. Thrill and bruit over thyroid vessels; characteristic when present. | 4. Not so. |
| 5. Toxicity—Appears with goiter. | 5. Goiter years before toxicity. |
| (a) Develops rapidly; high degree quickly reached. | (a) Toxic symptoms develop slowly, always milder. |
| (b) Tendency to remissions; crises. | (b) No remissions; no crises. |
| (c) Fatigue, hunger, loss of weight; early and prominent features. | (c) All later; never so prominent; sometimes not observed. |
| (d) Digestive disturbance, such as diarrhea, etc., frequent. | (d) Rare. |
| (e) Mental symptoms often marked. | (e) Not so. |
| 6. Blood pressure—average 140/60. | 6. Higher; average 160/100. |
| 7. Surface heat increased. | 7. Not so. |
| 8. B. M. R.—50 to 100 per cent plus. | 8. Lower—25 to 50 per cent plus. |
| 9. Occurs at all ages, even in childhood; most frequent in early adolescence. | 9. Rarely seen before fourth decade. |
| 10. Marked lymphocytosis. | 10. Normal blood picture. |
| 11. Iodin therapy helpful—temporarily. | 11. Aggravated by iodin therapy. |

count is often below 5000 and the lymphocytosis above 40 per cent.

This characteristic finding may be modified by several different factors, the most common of which undoubtedly is the coexistence of some acute inflammatory process. Here the leukopenia may be replaced by leukocytosis; but even in such case a certain degree of lymphocytosis will often be found to persist.

Again, the blood picture is unquestionably altered in many cases by treatment undergone before the examination is made. It is impossible to estimate the extent to which it may be modified by iodin therapy; we know that it may be profoundly modified by radiation therapy. The famous statement of a well-known surgeon that he rarely saw a case of gastric ulcer until it had been "cured" several times by the internist might well be paraphrased to apply with equal force to toxic goiter.

In toxic adenoma, when uncomplicated, the blood picture is as a rule entirely normal. The important matter to remember in this connection is the great frequency with which the adenomatous thyroid contains areas of hyperplasia as well. This is found to be true so uniformly in the specimens coming to the laboratory that one pathologist tells me he regards it as the usual condition. Obviously, should the hyperplastic elements predominate, a normal blood picture could scarcely be expected.

Attention is called to this particular point, not because it is new or infallible, but because it has been so long neglected. My own conclusion with reference to it may be stated very emphatically, that careful study of the blood picture in toxic goiter will give valuable aid in many cases and should never be omitted.

### IODIN THERAPY—ITS USE AND ABUSE

*Iodin Therapy.*—There is unity of opinion as to the beneficial action of iodin properly administered in true hyperplastic goiter. There is, however, some disagreement as to its detrimental action in toxic adenoma, though the weight of authority is largely in favor of this view. Personally I have no doubt upon the subject, because I have seen very many cases of toxic adenoma in which a mild degree of toxicity had been greatly increased by iodin medication, and I have seen very few in which it appeared to be at all beneficial. This conflict of opinion is probably due to failure to recognize that the two types of pathology are often associated in the same gland. The mere presence of palpable nodules in a hyperactive goiter does not warrant a dogmatic diagnosis of toxic adenoma.

The routine use of iodin as a differential test, therefore, is not to be recommended. If, after the several other diagnostic points have been elicited and duly weighed, there is still uncertainty, iodin in small dosage may be cautiously administered, the patient being kept under close observation and the drug promptly discontinued if unfavorable results appear.

Assuming, then, that there is a real difference in the effect of iodin medication in the two varieties of toxic goiter—that in one it is distinctly, though only temporarily beneficial, while in the other it is apt to prove harmful—their differential diagnosis becomes a matter of great and far-reaching importance.

While not strictly pertinent, a few additional comments in this connection may be pardoned. Iodin is an invaluable remedy in the treatment of goiter when used with discrimination. But the promiscuous routine employment of the agent so widely prevalent at the present time constitutes at once the greatest difficulty and the greatest menace of the entire goiter problem. Not only is it responsible for confusion, often hopeless, in the matter of accurate differential diagnosis, but it has added appreciably to the sum of unnecessary ill health and probably also to the total of preventable deaths. The records of hospitals and clinics, where goiter cases are seen in considerable number, uniformly show that the average duration of toxic symptoms before surgery is sought has increased tremendously. Since Lugol's

solution became a familiar household remedy, these patients are coming to operation only after irremediable damage has been done to the vital organs and the margin of surgical safety definitely lowered. Increase in primary and in postoperative mortality loom as probable consequences. Added to this is the commonly observed fact that restoration to normal health is always slow and often far from complete. Permanent invalidism follows in many instances.

For this deplorable state of affairs the public itself is responsible. The tendency to accept as gospel truth anything read on health questions, regardless of its source, seems to be a general weakness of human nature; and the inclination to indulge in self-medication is a well-recognized companion weakness. But our own profession is by no means blameless. Many physicians advise or prescribe iodin indiscriminately—for no better reason apparently than that their hapless patients appear to have goiters. In the past five years, in very few cases observed by me, either in clinic or in private practice, has the clinical picture not been modified and the diagnosis beclouded by previous iodin medication.

There is no mystery and should be no uncertainty about the use of iodin in the treatment of goiter. Let us do our part to stop its abuse.

## CONCLUSIONS

1. Exophthalmic goiter and toxic adenoma are distinct types of thyroid disease.

2. Differential diagnosis is always possible in typical cases. Mixed cases may present considerable difficulty.

3. Aside from scientific interest it is important to make the differentiation in every case because proper choice of treatment is at stake.

4. The prevalent universal use of iodin therapy is at once a menace and a reproach.

727 West Seventh Street.

## DISCUSSION

PHILIP K. GILMAN, M. D. (350 Post Street, San Francisco).—Doctor Cooke has well expressed the generally accepted ideas regarding toxic conditions of the thyroid gland. His aim at simplicity of classification is to be commended; that all will agree with him is not to be expected. Until we have one based upon an exact knowledge of etiology perhaps a universally accepted classification will be impossible.

From a clinical standpoint the segregation of goiter into either toxic or nontoxic is satisfactory. Subdivision of the toxic variety into exophthalmic and toxic adenomas is perhaps less definite. As with tumors, both connective tissue and epithelial, it is possible to arrange a series at one end of which the growth is definitely malignant and at the other end definitely benign with intermediate types which it is difficult, if not impossible, to classify as either benign or malignant. So with goiter we find definite hyperplastic conditions at one end of a series and definite so-called toxic adenomatous glands at the other, with mixed types not so readily segregated.

In our experience this lack of definite anatomical differentiation at times applies to clinical differentiation. Clinical differentiation is not always clear. We have observed exophthalmos in exceptional instances of toxic adenoma; and a uniform goiter, quite symmetrical, the seat of a diffuse adenomatosis. Differentiation by the administration of iodin is not absolute, as occasionally cases of toxic adenoma show definite improvement under its use. As Doctor Cooke well states, where both types of pathology are present in the same gland, clinical differentiation may also be very difficult. Cases of adenomatosis histologically proven, at times give symptoms attributable to the hyperplastic type.

Doctor Cooke is to be congratulated upon calling attention to the blood picture as an aid in differential diagnosis between these two types of toxic thyroid. Too little attention has been given to this point.

Doctor Cooke closes his readable and instructive paper with this sentence, "The prevalent universal use of iodin therapy is at once a menace and a reproach." Amen. Iodin does not cure. Iodin is one of the most valuable—if not the most valuable—single means we have in the preoperative preparation of a hyperplastic goiter patient if the patient has not been previously allowed or ordered to misuse it. I feel inclined to amend this closing sentence of Doctor Cooke's paper by suggesting the substitution of *misuse* for use.

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CARL L. HOAG, M. D. (177 Post Street, San Francisco).—Doctor Cooke has done well to select the simplest classification of goiter for clinical use, and has accurately pointed out the main differences between the typical hyperplastic (exophthalmos) and the adenomatous groups. Well-defined cases of either kind are not difficult to differentiate from each other. It must be remembered, however, that about 30 per cent of the hyperplastic goiters have no exophthalmos or bruit when they present themselves for treatment. Contrary to the typical type they frequently have a hard, nodular, irregular gland. This irregularity is due to an enlargement of the various lobules without a corresponding increase in the intervening septa. These nodules feel like multiple adenoma, and frequently cannot be distinguished from them. Just why an exophthalmos and a bruit do not develop in these cases has caused much speculation. Personally I believe that those developing most rapidly are most likely to have exophthalmos, those coming more slowly may permit the body to adjust itself to the toxic influence, just as a chronic infection gives no fever while acute processes produce the most marked reaction. On the other hand, these so-called cases of hyperplastic goiter without exophthalmos may eventually prove to be more accurately classed under the heading of thyroiditis. We are familiar with the iron-hard (iron-hard strumitis) cases of thyroiditis, but know less about the more chronic types of reaction.

How are we to distinguish between the cases of hyperplasia (or thyroiditis) from the adenomas? Probably the degree of toxicity helps most, as a high basal metabolic rate suggests hyperplasia. The adenomas seldom give a basal metabolic rate of more than plus fifty, even in most extreme cases. If small doses of iodin over a short period of time fail to decrease the symptoms hyperplasia is less probable. I agree with Doctor Cooke that the adenomas are not benefited but usually aggravated by iodin therapy. Iodin seems to have little or no effect in thyroiditis.

There can be no doubt that cases of mixed hyperplasia and adenoma do exist together. However, I think these cases are relatively uncommon, and when present the one is usually incidental to the predominating type in the clinical picture.

I have not found the blood count sufficiently constant to be of any aid in diagnosis.

Psychic instability (particularly crying) in my experience has been the first symptom of toxicity in many cases of adenoma.

A hemorrhage into a silent adenoma may precipitate toxicity with the usual sequence of symptoms.

I heartily agree with Doctor Cooke in all of his conclusions.

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A. S. LOBINGIER, M. D. (716 Merritt Building, Los Angeles).—The degree of toxicity in the forms of goiter under consideration cannot be explained by our

present knowledge of their relative histologic structure. I remember Theodor Kocher (when I was with him) attached the greatest importance to the study of the histogenesis of toxic goiter in arriving at a proper classification. But the biochemistry of this disease has yet to be satisfactorily worked out, and our present knowledge of it leaves much to be desired. The very fact that a hypertoxic thyroid may contain adenomata and that an adenomatous thyroid may contain areas of so-called hyperplastic structure, which may greatly modify the symptoms, lends confusion to any categorical effort in classification. Until we have a better histologic or chemical basis for definite differentiation in these two major clinical forms of toxic goiter, the ones given by the author and generally accepted must suffice.

From what we do know it is obvious that one who would successfully treat this disease of the thyroid gland must have given years of thoughtful study to the subject and have acquired a seasoned judgment based on a large clinical experience with toxic goiters. One can only wonder at the casual manner in which the empiricist will reach for Lugol's solution, or advise and undertake operation with little or no preliminary study or preparation of the patient for operation. Irreparable damage may be done to a patient who might otherwise have been a favorable subject for surgery, by the prolonged and unintelligent use of iodin. Such a patient cannot be reëstablished by the resumption of iodin preparation, and a patient who might have been a favorable risk, if iodin had not been given at all or if only given for the usual preparatory period, has been changed into a very hazardous risk by excessive iodinization. The author has placed a very proper emphasis upon this abuse of iodin.

The hot, smooth, soft, pulsating tumor; the thrill, the digital tremor and moist palms, the nervous, restless, anxious attitude—it is not necessary to have exophthalmos to properly classify the form of goiter from which this young patient is suffering. The nodular tumor of slow development without remissions, but with high blood pressure and metabolic rate under 50 with toxic symptoms coming on late, may easily be named an adenomatous goiter. Between these extremes of definite symptomatology are the cases in which a modifying histology as well as symptomatology will form a more or less confusing picture.

Every case of toxic goiter must be individually studied. The class in which its anatomical structure, predominating symptoms and laboratory tests place it will determine for the experienced surgeon the method of treatment which will offer the patient the safest and surest relief.

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## X-RAY THERAPY IN DERMATOLOGY *

*By* LOUIS F. X. WILHELM, M. D.
*Los Angeles*

DISCUSSION *by H. J. Ullmann, M. D., Santa Barbara; Douglass W. Montgomery, M. D., San Francisco; Irving R. Bancroft, M. D., Los Angeles.*

THE epoch-making discovery of x-rays by Conrad Roentgen [1] in 1894 and the publication of his work in 1895 was followed by a period devoted to a study of their practical application in medicine. Soon it was found that x-rays were of value in the treatment of skin diseases. Various parts of the world reported new indications for their use. Freund and Schiff [2] in Vienna, Walsh,[3] Morris [4] and Sequeira [5] in England, Oudin, Barthelmy and Darier [6] in France, and Pusey [7] and Williams [8] in this country were pioneers in this promising new field of therapy. For a number of years the use of x-ray therapy was increased so as to include almost every type of dermatologic condition. In fact roentgenologists were ready to apply x-ray treatment to every skin lesion without even attempting a diagnosis. Then quite suddenly the x-ray almost was thrown into discard on account of many disagreeable complications due to the want of measured dosage. The introduction of the Coolidge vacuum tube and the perfection of a reliable ammeter and voltmeter soon followed. These instruments combined with Wehnelt and Benoist's penetrometer, Sabouraud-Noire pastilles. Holzknecht and Corbet's radiometers allowed direct measurement of current. MacKee and Remer,[9] using these aids to standardization, evolved the method of indirect dosage now in general use. The MacKee [10] skin unit is the amount of x-ray necessary to cause a temporary epilation of the scalp hair. It is four-fifths of the minimum erythema dose.

### PATHOLOGY

The pathology of x-ray therapy of the skin was studied by Highman and Rulison [11] of New York. The elastic tissue, the glands, and the normal proliferative power of the skin are affected. The arterioles lose their elasticity and the corium tends to atrophy. The effect of x-ray therapy on the skin parallels from beginning to end the picture of scleroderma and, if more marked, the picture of xeroderma pigmentosum. These pathologic changes are slowly progressive and usually require years to develop to the fullest degree. Epithelioma is in a large percentage of instances the ultimate change.

The impression has obtained for many years that blonds are more susceptible to x-ray therapy than brunettes. The appearance of marked pigmentation following one-fourth skin unit (MacKee) of x-ray in several brunettes prompted the interesting paper of MacKee and Eller [12] on the variation of skin tolerance. One of these patients, a brunette about twenty-five years old, was treated at the Vanderbilt Clinic, New York. Following this reaction we treated three areas of skin one centimeter square on her forearm with one-fourth, one-half and three-fourths skin units x-ray and found pigmentation in each area. Subsequently toleration tests were carried out in 210 patients and over 40 per cent showed some pigmentation following one-fourth skin unit (MacKee) x-ray. MacKee and Eller conclude that there is a considerable variation of susceptibility to x-rays caused by age, location, complexion and inaccurracies of the best technique. Patients should be inspected carefully during a course of x-ray treatments for premonitory signs of reaction, for even a mild reaction may be followed occasionally by undesirable late effects.

### INDICATIONS AND LIMITATIONS

The experience gained from years of study of the effects of x-ray treatment has taught us some limitations as well as contraindications to its use. While originally the x-ray alone was employed in the treatment of many skin diseases, today we look upon x-ray as only a part of our treatment

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